

in which

Z is CH_3 , CH_2Hal in which Hal stands for a halogen atom or CH_2SCH_3 ; and

R_2' or R_3' are each, independently, H, lower alkyl, lower alkanoyl, benzoyl, benzoyl substituted by lower alkyl, lower alkoxy, or halogen or when taken together are lower alkylidene where the hydroxy groups are free or lower alkanoyl or benzoyl esters thereof.

Also disclosed are processes for their manufacture, pharmaceutical compositions and methods for using said compounds and compositions.

The compounds have highly desirable central nervous system and antihypertensive properties.

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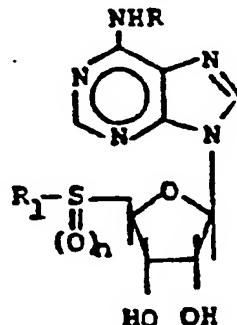
N⁶-SUBSTITUTED DEOXYRIBOSE ANALOGS OF ADENOSINES

Dutch patent application 67:14189 describes N⁶-cycloalkyl adenosines as cardioactive compounds. US Patent 3,851,056 discloses adenosines having an N⁶-

5 substituent of the formula -CH-CH₂-
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CH₃

antilipolytic and antihyperlipaemic properties.

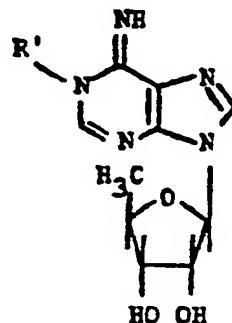
5'-Deoxy-5'-mercaptop-N⁶-(lower alkyl or benzyl) adenosines are described as antiviral agents in US Patent 3,575,959. US Patent 4,373,097 describes
10 compounds of the formula



wherein n is 0, 1, or 2, R₁ is alkyl and R is hydrogen, aliphatic or aromatic acyl. These compounds are disclosed as having antiinflammatory
15 and analgesic activity.

5'-Deoxy-5'-alkylthio-N⁶-(saturated or unsaturated, straight or branched aliphatic hydrocarbon)adenosines having blood pressure reducing and blood vessel dilating activity are
20 described in US patent 3,475,408.

5'-Deoxyribose derivatives of the formula

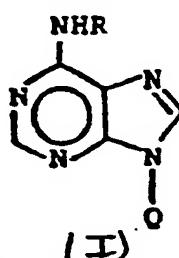


have been described in Japanese patent publication Number 55 8162-598 for treating thrombosis and 5 embolisms.

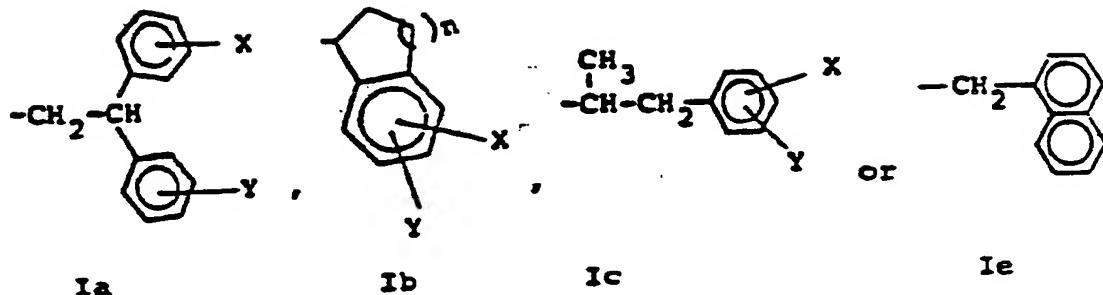
N⁶-Bicyclo[2.2.1]heptyladenosines having a 5' modified ribose having analgesic and antiinflammatory properties is disclosed in US Serial Number 665,216 now having a CIP copending with this 10 application. Finally, N⁶-(1- and 2-benzocyclo-alkyl)adenosines are disclosed in US 4,501,735.

The present compounds describe N⁶-substituted deoxyribose analogs of adenosines as having analgesic, neuroleptic, and antihypertensive activity. The 15 analogs include 5'-deoxygen, 5'-deoxy-5'-methylthio, and 5'-deoxy-5'-haloadenosines.

Accordingly, the present invention relates to a 20 compound of the formula (I)

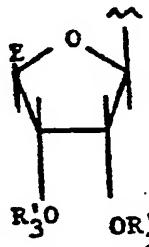


wherein R is cycloalkyl having a three to an eleven membered ring, or a group of the formula



in which n is one, two, or three; X and Y are each independently H, lower alkyl, hydroxy, lower alkoxy, benzyloxy, nitro, amino, trifluoromethyl, or halogen;

5 Q is. the formula



wherein Z is CH_3 , CH_2Hal , or CH_2SCH_3 ; R_2' or R_3' are each independently H, lower alkyl, lower alkanoyl, benzoyl, benzoyl substituted by lower alkyl, lower alkoxy, or halogen, or when taken together are lower alkylidene, such as isopropylidene; or lower alkanoyl or benzoyl esters thereof; its diastereomers or mixtures thereof, or a pharmaceutically acceptable acid addition salt thereof.

The present invention also relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the above Formula I with a pharmaceutically acceptable carrier, and to a method of treating mammals by administering to such mammals a dosage form of a compound of the Formula I as defined above.

In the compounds of the Formula I, the term "lower alkyl" is meant to include a straight or branched alkyl group having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, amyl, isoamyl, neopentyl, hexyl, and the like.

Hal or halogen includes particularly fluorine, chlorine or bromine.

Lower alkoxy is O-alkyl of from one to six carbon atoms as defined above for "lower alkyl".

Lower alkanoyloxy is a straight or branched

O
||
-C-alkyl group of from 1 to 6 carbon atoms in the alkyl chain as defined above.

The compounds of Formula I are useful both in the free base form and in the form of acid addition salts. Both forms are within the scope of the invention. In practice, use of the salt form amounts to use of the base form. Appropriate pharmaceutically acceptable

salts within the scope of the invention are those derived from mineral acids such as hydrochloric acid and sulfuric acid; and organic acids such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like, giving the hydrochloride, sulfamate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like, respectively.

The acid addition salts of said basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which

case the salt separates directly or can be obtained by concentration of the solution.

The compounds of the invention may contain asymmetric carbon atoms. The invention includes the 5 individual diastereomers and mixtures thereof. The individual diastereomers may be prepared or isolated by methods known in the art.

A preferred embodiment of the present invention is a compound of the Formula I, wherein R is of the 10 Formula Ia and X, Y, Q, R₂', R₃', and R₅' are as defined above or a pharmaceutically acceptable salt thereof.

Another preferred embodiment is a compound of Formula I wherein R is of the Formula Ia, X, and Y are 15 hydrogen, and Q, R₂', R₃', and R₅' are as defined above.

Another preferred embodiment is a compound of Formula I where R is of the Formula Ia, X, and Y are hydrogen, and Q is 5'-deoxy- β -D-ribose, 5'-deoxy-20 5'-methylthio ribose, or 5'-deoxy-5'-chloro ribose and R₂' and R₃' are each independently hydrogen, acetyl, benzoxy, benzoyl substituted by lower alkyl, lower alkoxy, halogen, or when taken together are alkylidene, particularly popropylidene.

25 A particular embodiment includes 5'-deoxy-N⁶-(2,2-diphenylethyl)adenosine or a pharmaceutically acceptable salt thereof.

A particular embodiment includes 5'-deoxy-5'-methylthio-N⁶-(2,2-diphenylethyl)adenosine 30 or a pharmaceutically acceptable salt thereof.

A particular embodiment includes 5'-deoxy-5'-chloro-N⁶-(2,2-diphenylethyl)adenosine or a pharmaceutically acceptable salt thereof.

A second generic embodiment of the present 35 invention is a compound of the Formula I, wherein R is of the Formula Ib and X, Y, Q, R₂, R₃, and R₅ are

as defined above or a pharmaceutically acceptable salt thereof.

Another second generic preferred embodiment is a compound of Formula I wherein R is of the Formula Ib,

5 X and Y are hydrogen, and Q, R₂', R₃', and R₅' are as defined above.

Still another second generic preferred embodiment is a compound of Formula I where R is of the Formula Ib, X and Y are hydrogen, and Q is

10 5'-deoxy- β -D-ribose, 5'-deoxy-5'-methylthio ribose, or 5'-deoxy-5'-chloro ribose or acetyl esters thereof and R₂' and R₃' are each independently hydrogen, acetyl, benzoyl, or when taken together are isopropylidene.

15 A particular embodiment of the compounds of Formula I wherein R₁ is of the Formula Ib includes 5'-deoxy-N⁶-(1-indanyl)adenosine or a pharmaceutically acceptable salt thereof.

20 A particular embodiment includes 5'-deoxy-5'-methylthio-N⁶-(1-indanyl)adenosine or a pharmaceutically acceptable salt thereof.

A particular embodiment includes 5'-deoxy-5'-chloro-N⁶-(1-indanyl)-adenosine or a pharmaceutically acceptable salt thereof.

25 A third generic embodiment of the present invention is a compound of the Formula I, wherein R is of the Formula Ic and X, Y, Q, R₂', R₃', and R₅' are as defined above or a pharmaceutically acceptable salt thereof.

30 Another preferred third generic embodiment is a compound of Formula I wherein R is of the Formula Ic, X and Y are hydrogen, and Q, R₂', R₃', and R₅' are as defined above.

35 Still another preferred third generic embodiment is a compound of Formula I where R is of the Formula Ic, X and Y are hydrogen, and Q is 5'-deoxy- β -D-ribose,

5'-deoxy-5'-methylthio ribose, or 5'-deoxy-5'-chloro-ribose or acetyl esters thereof and R_{2'} and R_{3'} are each independently hydrogen, acetyl, benzoyl or when taken together are isopropylidene.

5 A particular embodiment of the compounds of the Formula I wherein R is of the Formula Ic includes 5'-deoxy-N⁶-(1-methyl-2-phenylethyl)adenosine or a pharmaceutically acceptable salt thereof.

10 A particular embodiment includes 5'-deoxy-5'-methylthio-N⁶-(1-methyl-2-phenylethyl)adenosine or a pharmaceutically acceptable salt thereof.

A particular embodiment includes 5'-deoxy-5'-chloro-N⁶-(1-methyl-2-phenylethyl)adenosine or a pharmaceutically acceptable salt thereof.

15 A fourth generic aspect of the present invention is a compound of the Formula I, wherein R is cycloalkyl having three to eleven ring members, and Q, R_{2'}, R_{3'}, and R_{5'} are as defined above or a pharmaceutically acceptable salt thereof.

20 A preferred fourth generic aspect is a compound of Formula I wherein R is a 5-7 membered cycloalkyl radical, and Q, R_{2'}, R_{3'}, and R_{5'} are as defined above.

Another preferred fourth generic aspect is a 25 compound of Formula I wherein R is a 5-7 membered cycloalkyl radical, and Q is 5'-deoxy-³-D-ribose, 5'-deoxy-5'-methylthio ribose, or 5'-deoxy-5'-chloro ribose or acetyl esters thereof and R_{2'} and R_{3'} are each independently hydrogen, acetyl, 30 benzoyl, or when taken together are isopropylidene.

A particular embodiment of the compounds of the Formula I wherein R is of the Formula Id is 5'-deoxy-N⁶-(cyclopentyl)adenosine or a pharmaceutically acceptable salt thereof.

35 A particular embodiment includes 5'-deoxy-5'-methylthio-N⁶-(cyclopentyl)adenosine or a pharmaceutically acceptable salt thereof.

R_3' , and R_5' are as defined above or a pharmaceutically acceptable salt thereof.

A preferred fourth generic aspect is a compound of Formula I wherein R is a 5-7 membered cycloalkyl radical, and Q, R_2' , R_3' , and R_5' are as defined above.

Another preferred fourth generic aspect is a compound of Formula I wherein R is a 5-7 membered cycloalkyl radical, and Q is 5'-deoxy- β -D-ribose, 10 5'-deoxy-5'-methylthio ribose, or 5'-deoxy-5'-chloro ribose or acetyl esters thereof and R_2' and R_3' are each independently hydrogen, acetyl, benzoyl, or when taken together are isopropylidene.

A particular embodiment of the compounds of the 15 Formula I wherein R is of the Formula Id is 5'-deoxy- N^6 -(cyclopentyl)adenosine or a pharmaceutically acceptable salt thereof.

A particular embodiment includes 5'-deoxy-5'-methylthio- N^6 -(cyclopentyl)adenosine or a pharmaceutical 20 acceptably acceptable salt thereof.

A particular embodiment includes 5'-deoxy-5'-chloro- N^6 -(cyclopentyl)adenosine or a pharmaceutical acceptably acceptable salt thereof.

A fifth generic embodiment of the present invention is a compound of the Formula I, wherein R is of 25 the Formula Ie and X, Y, Q, R_2 , R_3 , and R_5 are as defined above or a pharmaceutically acceptable salt thereof.

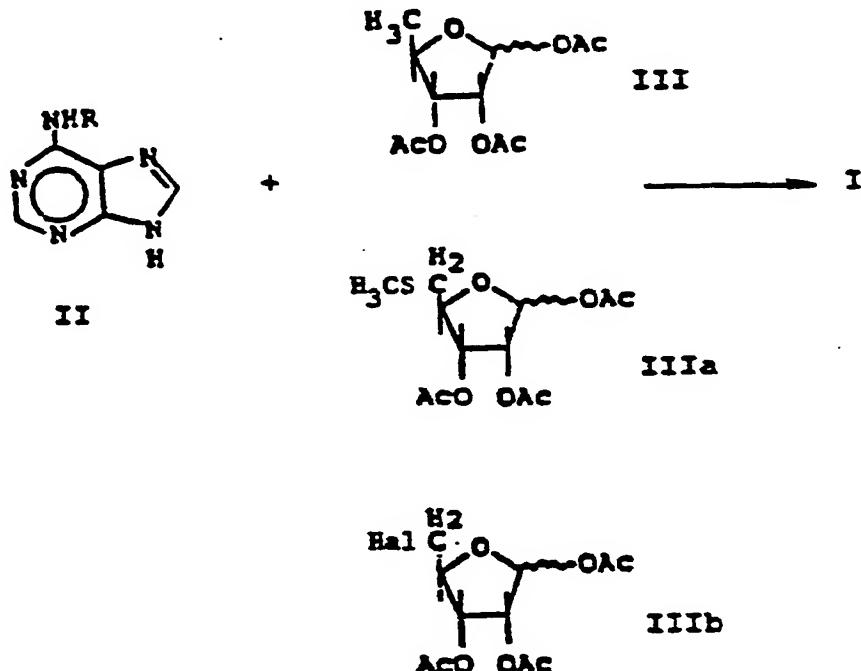
Another fifth generic preferred embodiment is a 30 compound of Formula I wherein R is of the Formula Ie, X and Y are hydrogen, and Q, R_2' , R_3' , and R_5' , are as defined above.

Still another fifth generic preferred embodiment is a compound of Formula I where R is of the Formula 35 Ie, X and Y are hydrogen, and Q is 5'-deoxy- β -D-ribose, 5'-deoxy-5'-methylthio-ribose, or 5'-deoxy-5'-chloro ribose or acetyl esters thereof and R_2'

and R_3' are each independently hydrogen, acetyl, benzyl, or when taken together are isopropylidene.

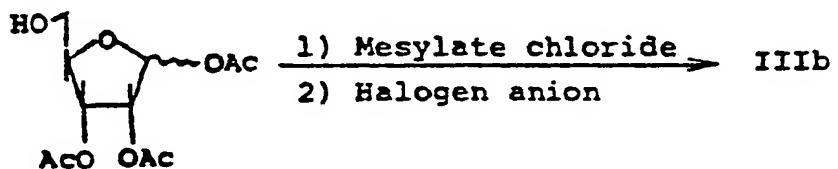
A particular embodiment of the compounds of Formula I wherein R_1 is of the Formula Ie includes 5 N^6 - α -naphthylmethyl-5'-deoxyadenosine or N^6 - α -naphthylmethyl-5'-deoxyadenosine-2',3'-di-O-acetyl.

The compounds of Formula I may be conveniently synthesized by reacting the appropriate N -6-substituted purine II with the protected deoxy sugar III, 10 IIIa, or IIIb as follows:



Compounds of Formula II where R is as defined above is reacted with compound of Formula III, IIIa, or IIIb in a neat melt and heating for approximately 1 to 12 hours. Addition of an acid in a catalytic amount 5 is useful.

The compounds of Formula IIIb may be prepared by the following scheme:

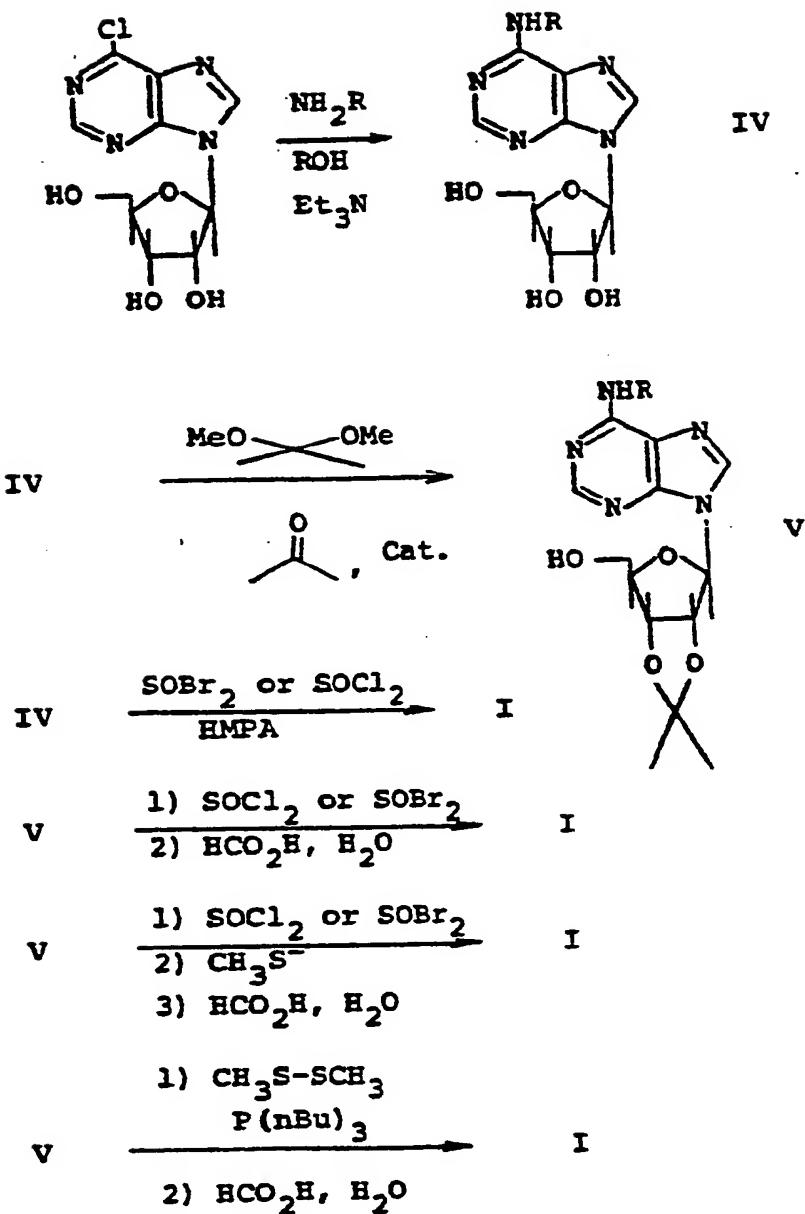


They may also be synthesized from the known 6-chloro-10 purineriboside as shown in Scheme I.

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SCHEME 1



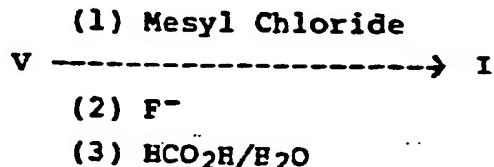
Compounds of Formula IV are made by reacting 6-chloropurine-riboside with the amine NH_2R where R is as defined above, in an inert solvent and in the presence of a base such as triethylamine.

- 5 Compound IV can be converted to the isopropylidene analog V by reacting with 2,2-dimethoxypropane in acetone and in the presence of an acid catalyst such as bis-(p-nitrophenyl)phosphate hydrate (Hampton's reagent). The 5'-deoxy-5'-chloro and 5'-deoxy-5'-bromo compounds of Formula I are synthesized by reacting the appropriate Compound V with thionyl chloride or thionyl bromide followed by treatment with formic acid and water to remove the isopropylidene and give Compound I. Compounds of Formula I may also
- 10 be obtained by directly treating IV with thionyl chloride or thionyl bromide in hexamethyl phosphoamide (HMPA).
- 15

The 5'-deoxy-5'-methylthio adenosine compounds are prepared in one of two ways. The N^6 -substituted 5'-deoxy-5'-chloro adenosine isopropylidene compound can be treated with thiomethoxide to displace the chloro moiety, followed by formic acid-water deprotection to yield compounds of Formula I. Alternatively, a compound of Formula V can be treated with dimethyldisulfide in the presence of tri-n-butylphosphine, followed by formic acid-water deprotection, to give compounds of Formula I where Z is CH_2SCH_3 .

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- 25
- 30

Additionally, the compounds of Formula I wherein Z is F may be prepared by the following reaction:



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The compounds of Formula I have been found to possess differing affinities for adenosine receptors (designated A₁ and A₂ receptors for convenience). These compounds are active in animal tests which are 5 predictive of neuroleptic activity for the treatment of major psychoses such as schizophrenia. These compounds also have analgesic properties and as such, are useful in the treatment of pain.

In addition, the compounds of the present invention are useful as antihypertensive agents for the 10 treatment of high blood pressure.

PHARMACOLOGICAL EVALUATION

Adenosine Receptor Binding - A₁ Receptor Affinity (RBA₁)

15 Preparation of Membranes

Whole brain minus cerebellum and brainstem from male Long Evans rats (150-200 g) was homogenized in 30 volumes of ice-cold 0.05 M Tris-HCl buffer pH 7.7 using a Brinkman Polytron PT-10, (setting number 6 20 for 20 seconds) and centrifuged for ten minutes at 20,000 x g (Sorvall RC-2), 4°C. The supernatant was discarded, and the pellet was resuspended and centrifuged as before. The pellet was resuspended in 20 ml Tris-HCl buffer containing two International 25 Units/ml of adenosine deaminase (Sigma type III from calf intestinal mucosa), incubated at 37°C for 30 minutes, then subsequently at 0°C for ten minutes. The homogenate was again centrifuged, and the final pellet was resuspended in ice-cold 0.05 M Tris-HCl 30 buffer pH 7.7 to a concentration of 20 mg/ml original wet tissue weight and used immediately.

Assay Conditions

Tissue homogenate (10 mg/ml) was incubated in 0.05 M Tris-HCl buffer pH 7.7 containing 1.0 nM [³H]-N⁶-cyclohexyladenosine ([³H]-CHA) with or 5 without test agents in triplicate for one hour at 25°C. Incubation volume was 2 ml. Unbound [³H]-CHA was separated by rapid filtration under reduced pressure through Whatman glass fiber (GF/B) filters. The filters were rinsed three times with 5 ml of ice 10 cold 0.05 M Tris-HCl buffer pH 7.7. The radio-labeled ligand retained on the filter was measured by liquid scintillation spectrophotometry after shaking the filters for one hour or longer on a mechanical shaker in 10 ml of Beckman Ready-Solv HP scintillation 15 cocktail.

Calculations

Nonspecific binding was defined as the binding which occurred in the presence of 1 mM theophylline. The concentration of test agent which inhibited 50% of 20 the specific binding (IC₅₀) was determined by nonlinear computer curve fit. The Scatchard plot was calculated by linear regression of the line obtained by plotting the amount of radioligand bound (pmoles/gram of tissue)

25 versus [bound radioligand] / [free radioligand]. Since

the amount of radioligand bound was a small fraction of the total amount added, free radioligand was defined as the concentration (nM) of radioligand added 30 to the incubation mixture. The Hill coefficient was

calculated by linear regression of the line obtained by plotting the log of the bound radioligand vs the log of the $\frac{\text{bound radioligand}}{\text{B}_{\max} - \text{bound radioligand}}$.

5 The maximal number of binding sites (B_{\max}) was calculated from the Scatchard plot.

Adenosine Receptor Binding - A₂ Receptor Affinity (RBA2)

Tissue Preparation

10 Brains from 200-500 g mixed sex Sprague-Dawley rats were purchased from Pel-Freez (Rogers, Arkansas). Fresh brains from male Long-Evans hooded rats (Blue Spruce Farms, Altamont, NY) gave essentially identical results. Brains were thawed and then kept on ice

15 while the striata were dissected out. Striata were disrupted in 10 vol of ice-cold 50 mM Tris-HCl (pH 7.7 at 25°C, pH 8.26 at 5°C) (Tris) for 30 seconds in a Polytron PT-10 (Brinkmann) at setting 5. The suspension was centrifuged at 50,000 xg for ten

20 minutes, the supernatant discarded, the pellet resuspended in 10 vol ice-cold Tris as above, re-centrifuged, resuspended at 1 g/5 ml, and stored in plastic vials at -70°C (stable for at least six months). When needed, tissue was thawed at room

25 temperature, disrupted in a Polytron, and kept on ice until used.

Incubation Conditions

All incubations were for 60 minutes at 25°C in 12x75 mm glass tubes containing 1 ml Tris with 5 mg 30 original tissue weight of rat weight of rat striatal

membranes, 4 nM [³H]-N-ethyl adenosine-5'-carboxamide ([³H]NECA), 50 nM N⁶-cyclopentyladenosine (to eliminate A₁ receptor binding), 10 mM MgCl₂, 0.1 units/ml of adenosine deaminase and 1% dimethylsulfoxide. N⁶-Cyclopentyladenosine was dissolved at 10 mM in 0.02 N HCl and diluted in Tris. Stock solutions and dilutions of N⁶-cyclopentyladenosine could be stored at -20°C for several months. Test compounds were dissolved at 10 mM in dimethylsulfoxide on the same day as the experiment, and diluted in dimethylsulfoxide to 100x the final incubation concentration. Control incubations received an equal volume (10 µl) of dimethylsulfoxide; the resulting concentration of dimethylsulfoxide had no effect on binding. [³H]NECA was diluted to 40 nM in Tris. The membrane suspension (5 mg/0.79 ml) contained sufficient MgCl₂ and adenosine deaminase to give 10 mM and 0.1 units/ml, respectively, final concentration in the incubation.

For test compounds with IC₅₀ values less than 1 µM, the order of additions was test compound (10 µl), N⁶-cyclopentyladenosine (100 µl), [³H]NECA (100 µl), and membranes (0.79 ml). For test compounds with IC₅₀ values greater than 1 µM and limited water solubility, the order of additions (same volumes) was test compound, membranes, N⁶-cyclopentyladenosine, and [³H]NECA. After all additions, the rack of tubes was vortexed, and the tubes were then incubated for 60 min at 25°C in a shaking water bath. The rack of tubes was vortexed an additional time halfway through the incubation.

Incubations were terminated by filtration through 2.4 cm GF/B filters under reduced pressure. Each tube was filtered as follows: the contents of the tube were poured onto the filter, 4 ml of ice-cold Tris were added to the tube and the contents poured onto

the filter, and the filter was washed twice with 4 ml of ice-cold Tris. The filtration was complete in about twelve seconds. Filters were put in scintillation vials, 8 ml of Formula 947 scintillation 5 fluid added, and the vials left overnight, shaken, and counted in a liquid scintillation counter at 40% efficiency.

Data Analysis

10 Nonspecific binding was defined as binding in the presence of 100 μ M N⁶-cyclopentyladenosine, and specific binding was defined as total binding minus nonspecific binding. The IC₅₀ was calculated by weighted nonlinear least squares curve-fitting to the mass-action equation.

15
$$Y = T - S \cdot \frac{D}{D + K}$$

where Y is cpm bound
T is cpm total binding without drug
S is cpm specific binding without drug
20 D is the concentration of drug
and K is the IC₅₀ of the drug

Weighting factors were calculated under the assumption that the standard deviation was proportional to the predicted value of Y. Nonspecific binding was treated 25 as a very large (infinite) concentration of drug in the computer analysis.

The IC₅₀ values (nM) for adenosine A₁ and A₂-receptor affinity are reported in the table.

<u>Example Number</u>	<u>Receptor Binding</u>	
	<u>RBA-1 (nM)</u>	<u>RBA-2 (nM)</u>
1	227	1110
2	1680	21200
5	40	5700
3	556	20000
4	16	17200
5	52	21400
6	51	6300
10	700	44000
7	9	7400
8	13	7200
10	660	2000
11	1490	58200
12	53	240
15	218	8650
13	3	1600
14	35	7900
15	2	2700
16	1.2	2800
20	1370	71300
18	1010	323
19	2520	NT*
21	607	NT
22	80	3040
25		

*NT = Not tested

ANTIPSYCHOTIC EVALUATION

The compounds of the invention are new chemical substances which are useful as pharmaceutical agents for the treatment of psychoses. The antipsychotic activity of representative compounds of the invention was established by the Mouse Activity and Screen Test Procedure (MAST) described below.

Animals

Nine unfasted Swiss-Webster male mice weighing 10 20-30 g are equally divided into three groups for each drug dose to be tested. That is, data for each dose level was generated by three separate groups of three mice each.

Drugs

15 A minimum of three dose levels (10, 30, and 100 mg/kg) are tested for each drug. Treatments are administered intraperitoneally one hour prior to testing. All dosages are calculated as parent compound and given in volumes of 10 ml/kg. Compounds 20 are dissolved or suspended in 0.2% Methocel. Control animals are injected with Methocel.

Testing: A two part testing procedure is started one hour postinjection. First, the screen test (ST) is performed (see Pharmac. Biochem. Behav. 6, 351-353, 25 1977). Briefly this test consists of placing mice on individual wire screens which are then rotated 180 degrees at the start of a 60 second observation period. The number of mice falling off the inverted screen is recorded.

30 Immediately following the screen test, the final phase of testing is initiated by placing each group of three mice in one actophotometer (Life Sciences, 22, 1067-1076, 1978). The actophotometer

consists of a cylindrical chamber whose center is occupied by another cylinder which contains the illumination for six photocells located on the perimeter of the chamber. Six light-beam interruptions 5 equal one count. Locomotor activity is recorded by computer at ten minute intervals for 60 minutes.

Data: The data obtained from the screen test are expressed as percent of mice falling off the screen. Data derived from locomotor activity of drug treated 10 mice are compared to the activity of vehicle treated animals and are expressed as percent inhibition of spontaneous locomotion. All percentages reported for inhibition of locomotion (LI) are based upon data accumulated for one hour. Both phases of testing are 15 graded: A=60-100%; C=31-59%; and N=0-30%. An overall dose rating is obtained by the following criteria:

	Inhibition of Locomotion Rating	with	Screen Test Failure Rating	=	Dose Rating
20	A	-	N or C	=	A
	A	-	A	=	C
	C	-	N or C	=	C
	All other combinations				= N

LAD refers to the lowest dose at which an A rating 25 is achieved. Compounds which exhibit an overall dose rating of A at a dose of 100 milligrams/kilogram or less are considered active. Utilizing this procedure, an overall dose rating of A was obtained for the noted compound at the indicated dose. The compounds are 30 identified in the Examples.

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Example	Dose (mg/kg)	Inhibition of Mouse Locomotor Activity		Screen Test Failure
5	1	3	29%	11%
		10	30%	0%
		30	65%	11%
10	2	10	16%	0%
		30	52%	0%
		100	80%	11%
15	3	10	19%	0%
		30	68%	22%
		100	96%	100%
20	4	10	-16%	0%
		30	20%	0%
		100	56%	0%
25	5	1	25%	0%
		3	58%	11%
		10	69%	22%
30		30	96%	100%
		100	99%	100%
35	6	1	12%	0%
		3	49%	0%
		10	83%	88%
		30	92%	99%

Example	Dose (mg/kg)	Inhibition of	Screen test
		mouse locomotor	failure
5	7	9%	0%
	30	-50%	0%
	100	38%	0%
8	7	22%	11%
	30	39%	0%
	100	29%	0%
10	9	1%	0%
	1.0	46%	0%
	3.0	36%	22%
	10	90%	77%
	30	92%	99%
	100	97%	99%
15	10	41%	0%
	30	78%	55%
	100	99%	99%
20	11	-4%	0%
	30	34%	0%
	100	90%	0%
12	3	44%	0%
	10	37%	0%
	30	59%	0%

Example	Dose (mg/kg)	Inhibition of mouse locomotor activity		Screen test failure
5	13	10	-13%	0%
		30	39%	11%
		100	63%	0%
10	14	10	57%	0%
		30	69%	0%
		100	96%	0%
15	15	10	65%	67%
		30	96%	100%
		100	100%	100%
16	16	10	2%	0%
		30	51%	11%
	15	100	-	-
20	17	0.3	44%	11%
		1.0	83%	55%
		3.0	95%	99%
25		10	89%	99%
		30	100%	99%
		100	100%	99%
18	18	0.1	12%	0%
		0.3	25%	11%
		1.0	39%	11%
25		3.0	52%	22%
		10	93%	78%
		30	94%	100%
		100	98%	100%

Example	Dose (mg/kg)	Inhibition of mouse locomotor activity	Screen test failure
5	19	36%	11%
	10	55%	0%
	30	83%	0%
10	20	-1%	0%
	10	49%	0%
	30	81%	0%
15	23	-2%	0%
	1	9%	0%
	1	7%	0%
	3	48	0%
	10	76	0%
	30	81	0%

A representative compound of the invention (identified in the Example 5) was also tested for antipsychotic activity according to the following protocol (SIDR). The noted compound has the indicated ED₅₀ values (mg/kg) and is considered active as an antipsychotic agent in the test procedure.

Procedure

Mature male Long-Evans rats or squirrel-monkeys are conditioned to push a lever in order to avoid a painful electric footshock. If the animal fails to push the lever, he receives a shock every ten seconds until the lever is pushed. Shocks can be terminated

by pushing the lever. Thereafter, as long as the lever is pushed at least once every 20 seconds, there will be no shock.

Each animal acts as its own control; one weekly 5 session is used to establish baseline behavior and another session later in the week is used as a drug session. Once patterns of avoidance are established, the effects of standard and unknown compounds are studied.

10 The compound (Example 5) had an ED₅₀ of 2.8 mg/kg for blockade of avoidance with a response of 10% at 4 mg/kg for blockade of escape.

ANTIHYPERTENSIVE EVALUATION (AHP3)

The usefulness of the compounds of the present 15 invention as antihypertensive agents is demonstrated by their effectiveness in standard pharmacological test procedures, for example, in causing a significant decrease in mean arterial blood pressure in the conscious rat. This test procedure is described in 20 the following paragraphs.

A Method for the Direct Monitoring of Aortic Blood Pressure and Heart Rate from Conscious Rats

The continuous monitoring of pulsatile blood pressure (BP) from unrestrained conscious rats 25 surgically equipped with polyethylene cannulas was accomplished by means of a computer assisted data capture scheme (CADCs). The basic elements of the methodology are the cannulation procedure and the CADCs.

Method

Cannulation Procedure: Rats were anesthetized with Telazol (1:1 tiletamine HCl and zolazepam HCl); 20-40 mg/kg IM and the descending aorta exposed via a 5 midline incision. Cannulas fabricated from polyethylene tubing were inserted into the aorta via an undersized puncture hole below the renal arteries. The puncture hole was made by a 23 G disposable needle with a section of the aorta clamped off above 10 and below the puncture site. The cannulas, consisting of a PE100 (0.86 mm ID) body and a PE50 (0.58 mm ID) tip, were attached to a trocar, inserted through the psoas muscle, and passed subcutaneously along the midline of the back and externalized between the ears. 15 The cannulas were anchored to the psoas muscle and between the scalulae (3-0 green braided suture). The midline incision was closed in two steps (muscle first, skin second) using continuous over-and over sutures (4-0 chronic). Each rat was then given 20 penicillin 30,000 units subcutaneously (Penicillin G Procaine Sterile Suspension).

The rats were fitted with a harness-spring-swivel assembly designed to protect the cannula and to provide the rat relative freedom of movement. The 25 harnesses were fabricated from nylon hook and loop tape cemented to a metal plate to which spring wires (18-8 stainless steel), were attached to brass swivels. Each polyethylene cannula was channeled through a spring and connected through a swivel to 30 a pressure transducer (Model P23Gb; Statham Instruments; Hato Rey, Puerto Rico) and an infusion pump (Sage model 234-7; Orion Research, Cambridge, MA) by means of PE100 tubing. While on test, each rat received a continuous slow infusion of heparinized 35 saline solution (approximately 400 l or 40 units of heparin per 24 hour period) to prevent clot

formation. Additional "flushes" of the cannula with heparinized saline were carried out when the aortic pulse pressure (systolic minus diastolic) was less than 25 mm Hg.

5 CADCS: The pulsatile blood pressure and heart rate of each of 32 rats was monitored every minute by means of two in-laboratory microcomputers communicating directly with a data concentrator computer. The data were first stored on the data concentrator disk 10 and then transferred to a magnetic tape for analysis and report generation by the main research computer. The overall scheme involved modulating the primary signal from the pressure transducer, generating the primary data set of the one-minute values for 15 systolic, diastolic, and mean blood pressures and heart rate by the in-lab microcomputer and the storage, analysis, and report generation by the main research computer.

The transducers were connected to analog signal 20 conditioning modules. The modules provided a regulated excitation voltage for the transducers, amplification as required to interface the microprocessors and an active low pass filter to compensate for the pressure wave form distortion 25 produced by the flexible, fluid filled, narrow cannula. The distortion was 22-26 Hz and this provided a reliable estimate of both systolic and diastolic blood pressure.

The microcomputers (one for each of two groups 30 of 16 rats) were connected to the input components through the module interface units, an analog-to-digital converter for the pressure wave form signal and the digital inputs for the dose and event marker switches. The microcomputer controlled the sequential 35 acquisition of data from the modular interface units

through an internal synchronous time-of-day clock/time base generator. Utilizing the time base generator as a reference, the blood pressure values and the marker switch status for each of the 32 stations were 5 sampled every ten msec. The microcomputer processed each blood pressure sample as it was received to produce "running average" values for heart rate, and mean, systolic and diastolic blood pressures.

When tested by the above procedure, the following 10 compounds produced the following changes in MAP (mean arterial pressure) and heart rate.

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EEG-1

-30-

Example Number	mg/kg	1	Hour				
			3	5	7	9	
2	10	MAP	+18%	+13	+ 4	+ 5	+ 9
		HR	+10%	0	+ 7	+14	+12
5	3	MAP	+17	+ 9	+ 6	+11	+ 6
		HR	+18	+ 9	+ 6	+ 5	+10
4	10	MAP	+ 2	+ 3	+15	+ 1	+ 8
		HR	+ 3	+ 9	+ 8	+17	+ 7
10	5	MAP	+36	+23	+20	+19	+18
		HR	+65	+60	+46	+39	+41
7	10	MAP	+8%	+5%	+8%	+10%	+5%
		HR	+4%	+5%	+16%	+25%	+12%
15	8	MAP	+24%	+14%	+4%	+1%	0%
		HR	+27%	+9%	+7%	+22%	+14%
20	9	MAP	+1%	+10%	+2%	+3%	+4%
		HR	+9%	+14%	+6%	+17%	+17%
20	30	MAP	+5%	+5%	+5%	+8%	+5%
		HR	+5%	+1%	+2%	+6%	+3%
20	10	MAP	+20%	+25%	+13%	+13%	+7%
		HR	+46%	+43%	+33%	+21%	+4%

0181129

EEG-1

-31-

Example	mg/kg	Hour							
		1	3	5	7	9			
		10	3	MAP	+11%	0%	+7%	+7%	+7%
				HR	+29%	+11%	+6%	+15%	+20%
5			10	MAP	+21%	+13%	+5%	+9%	+6%
				HR	+43%	+28%	+13%	+9%	+6%
		11	10	MAP	+3%	+2%	+2%	0%	+7%
				HR	+1%	+6%	+6%	+1%	+10%
10		12	10	MAP	+16%	+4%	+7%	+6%	+1%
				HR	+19%	+9%	0%	+6%	+4%
		14	10	MAP	+12%	+9%	+1%	+7%	+2%
				HR	+23%	+9%	0%	+3%	+17%
		15	10	MAP	+24%	+33%	+29%	+26%	+14%
				HR	+44%	+55%	+53%	+42%	+29%
15		16	10	MAP	+14%	+13%	+14%	+13%	+6%
				HR	+23%	+20%	+12%	+10%	+2%
		17	10	MAP	+42%	+41%	+37%	+36%	+32%
				HR	+64%	+64%	+61%	+58%	+53%
20		18	10	MAP	+43%	+30%	+23%	+26%	+23%
				HR	+63%	+58%	+47%	+45%	+40%

Example	mg/kg		Hour					
			1	3	5	7	9	
19	10	MAP	+32%	+20%	+20%	+20%	+12%	
		HR	+6%	+4%	+4%	+5%	+1%	
5	20	10	MAP	+16%	+15%	+15%	+15%	+15%
		HR	+15%	+19%	+13%	+15%	+9%	
	21	10	MAP	0%	+11%	+15%	+18%	+9%
		HR	+23%	+13%	+3%	+8%	+14%	
	22	10	MAP	+21%	+8%	+17%	+17%	+20%
10		HR	+7%	+23%	+8%	+14%	+8%	
	23	10	MAP	+3%	+5%	+4%	+4%	+16%
		HR	+19%	+11%	+6%	+8%	+15%	

ANALGESIC EVALUATION

The antiwrithing (AW) test provides preliminary assessment of compounds with potential analgesic activity. The test is performed in male Swiss-Webster mice. Compounds are administered subcutaneously in aqueous 0.2% methylcellulose or other appropriate vehicles in volumes of 10 ml/kg.

15 Dosages represent active moiety.

Acetic acid (0.6%, 10 ml/kg) is injected intraperitoneally 20 minutes after administration of the adenosine agonist. Writhing movements are counted for five minutes starting seven minutes after the 25 acetic acid injection. Writhing is defined as abdominal constriction and stretching of the body and hind legs with concave arching of the back.

Data are expressed as ED₅₀ values, where the ED₅₀ is the dose necessary to suppress writhing by 50% relative to vehicle controls. ED₅₀ values are calculated by nonlinear regression analysis. For example, 5'-deoxy-N⁶-cyclopentyladenosine, a representative compound shown as Example 5 of the present invention, had an ED₅₀ of 0.9 mg/kg when administered intraperitoneally to mice.

Also when administered intraperitoneally, the compound of Example 12 had an ED₅₀ of 3.0 mg/kg and 5'-chloro-N⁶-(R)phenylisopropyl adenosine (Example 15) had an ED₅₀ of 1.8 mg/kg when administered intraperitoneally.

Accordingly, the present invention also includes a pharmaceutical composition for treating psychoses, pain or hypertension comprising a corresponding antipsychotic, analgesic or antihypertensive effective amount of a compound of the Formula I as defined above together with a pharmaceutically acceptable carrier.

The present invention further includes a method for treating psychoses, pain or hypertension in mammals suffering therefrom comprising administering to such mammals either orally or parenterally a corresponding pharmaceutical composition containing a compound of the Formula I as defined above in appropriate unit dosage form.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be encapsulating material. In powders, the

carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 or 10 to about 70 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, 10 pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as 15 carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid 20 dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The 25 molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions. As an example may be 30 mentioned water or water propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component 35 in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous

suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium

5 carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral

10 administration. Such liquid forms include solutions, suspensions, and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient

15 solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon, or other volumetric container. When multiple liquid

20 doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain,

25 in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. The liquid utilized for preparing the liquid form preparation may

30 be water, isotonic water, ethanol, glycerine, propylene glycol, and the like as well as mixtures thereof. Naturally, the liquid utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts

35 of ethanol are not suitable for parenteral use.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage 5 form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or it can be the 10 appropriate number of any of these in packaged form.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 500 mg preferably to 5 to 100 mg according to the particular application and the potency of the active 15 ingredient. The compositions can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as described above, the mammalian dosage range for a 70 kg subject is from 0.1 to 150 mg/kg of body weight per day or preferably 20 1 to 50 mg/kg of body weight per day. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed.

Determination of the proper dosage for a particular 25 situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is 30 reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following Examples further illustrate the invention.

EXAMPLE 1

N⁶-[2,2-Diphenylethyl]-5'-deoxyadenosine

A mixture of the N⁶-(2,2-diphenylethyl)purine (31.5 g, 10 mmol) and the triacetate sugar III¹ (2.6 g, 5 mmol) was heated at 180°C. To this was added one microdrop of H₂SO₄ and melt stirred at 180-195°C for four hours. The melt cooled to room temperature, solidified. The solid dissolved in ethyl acetate and purified by silica gel flash chromatography. The new 10 compound was isolated by evaporation of solvent and placed in a solution of methanol (70 mL) and sodium methoxide (0.05 g, 1 mmol). The mixture was stirred at room temperature for four hours. The reaction quenched with Dowex 50 (H⁺ form) to pH = 6. The resin 15 was removed by filtration and the solvent removed in vacu to give a hygroscopic foam. The foam was coevaporated to dryness with Methanol, yield 0.26 g (8%): mp 185-187.5.

Anal (C₂₄H₂₅N₅O₃):

20 calc: C = 58.81, H = 5.61, N = 20.52,
found: C = 59.00, H = 5.32, N = 19.62.
¹H NMR (DMSO-d₆, 200 MHz): δ 1.2 (d, 3H), δ 3.9 (m, 2H), δ 4.1 (bs, 2H), δ 4.6 (m, 2H), δ 5.2 (d, 1H),
δ 5.4 (d, 1H), δ 5.8 (d, 1H), δ 7.1-7.3 (m, 10H),
25 δ 7.8 (bs, 1H), δ 8.3 (bs, 2H).

The starting purine was prepared as follows: a solution of 2,2-diphenylethylamine (7 g, 35.5 mmol), triethylamine (3.6 g, 35.5 mmol) and 6-chloropurine (5.5 g, 35.5 mmol) in ethanol (250 mL) was stirred at 30 reflux, overnight. The solution was cooled to room temperature. The precipitated solid was collected and washed with ethanol (100 mL). The off-white solid was

1. Kiss, J., D'Souza, R., Koereringe, J. A.,
Arnold, W.; Helv. Chim. Acta., 65, (5), 1522-1537
35 (1982).

dried in vacuo at room temperature; yield 6.5 g (58%);
mp = 232-233°C.

Anal. (C₁₉H₁₇N₅),
calc: C = 72.36, H = 5.43, N = 22.21;
5 found: C = 72.05, H = 5.42, N = 21.99

EXAMPLE 2

5'-[1-Indanyl]-5'-deoxyadenosine

The title compound was prepared as Example 1 using 2.5 g, 10 mmol of N⁶-(1-indanyl)purine and 10 4.0 g, 15 mmol of the triacetate-5-deoxy sugar. The hydrolysis used 0.25 g of sodium methoxide and yielded 0.7 g (19%) as an extremely hygroscopic syrup.

Anal. (C₁₉H₂₁N₅O₃):
calc: C = 62.11, H = 5.76, N = 19.06;
15 found: C = 60.67, H = 6.14, N = 18.26.
¹H NMR (DMSO-d₆, 90 MHz): δ 1.25 (d, 3H),
δ 2.0-2.2 (m, 2H), δ 2.8-3.1 (m, 2H),
δ 3.8-4.0 (m, 2H), δ 4.6 (m, 1H), δ 5.05 (d, 1H),
δ 5.3 (d, 1H), δ 5.8 (d, 1H), δ 5.8-6.0 (bs, 1H),
20 δ 7.0-7.3 (m, 4H), δ 7.9 (br.d, 1H), δ 8.15 (s, 1H), δ 8.2 (s, 1H).

The starting purine was prepared as in Example 5 using 1-aminoindane (1.3 g, 10 mmol), triethylamine (1.1 g, 10 mmol) and 6-chloropurine (1.5 g, 10 mmol); 25 yield 1.6 g (64%); mp = 247-248°Cd.

Anal. (C₁₄H₁₃N₅),
calc: C = 66.91, H = 5.21, N = 27.87;
found: C = 66.46, H = 5.26, N = 27.54.

EXAMPLE 3

30 (R)-N⁶-[Phenylisopropyl]-5'-deoxyadenosine

The reaction proceeded as in Example 1 with N⁶-[phenylisopropyl]purine (4.5 g, 17.8 mmol) and 4.6 g

(17.8 mmol) of the deoxy-sugar. The hydrolysis used 0.3 g of sodium methoxide and yielded 1.8 g (28%) hygroscopic solid, mp = ~ 70°C.

5 ^1H NMR (DMSO- d_6), 200 MHz): δ 1.1 (d, 3H), δ 1.2 (d, 3H), δ 2.7-2.8 (m, 1H), δ 3.0 (m, 1H), δ 3.95 (m, 2H), δ 4.5 (m, 2H), δ 5.2-5.6 (br.s, 2H), δ 5.9 (d, 1H), δ 7.0-7.2 (m, 5H), δ 7.6 (br.d, 1H), δ 8.3 (s, 1H), δ 8.5 (s, 1H).

10 The starting purine was prepared as follows: a solution of the L-amphetamine (13.6 g, 0.1 mmol) and 6-chloropurine (7.73 g, 0.05 mmol) in ethanol (250 mL) was stirred at reflux for 72 hours. The solution cooled to 45°C and the ethanol was removed in vacuo. The residue was poured into a mixture of chloroform 15 and water (100 mL). The organics were separated and dried over MgSO_4 and the solvent removed in vacuo to give a white solid which was dried in vacuo, at RT, overnight; yield 11 g (87%); mp = 190-193°C.

15 $\text{Anal (C}^{14}\text{H}_{15}\text{N}_5\text{)},$
20 calc: C = 66.38, H = 5.97, N = 27.65;
found: C = 66.10, H = 5.96, N = 27.14.
[α]_D = -114.8 (c 1.08, MeOH).

EXAMPLE 4

(S)-N⁶-[Phenylisopropyl]-5'-deoxyadenosine

25 The title compound was prepared as in Example 1 using 5.0 g, 19.7 mol of N⁶-(S)-phenylisopropylpurine and 5.2 g, 19.7 mol of the triacetate-5-deoxy sugar. The hydrolysis used 0.3 g sodium methoxide and yielded 1.3 g (19%) as an extremely hygroscopic syrup.

30 $\text{Anal (C}_{19}\text{H}_{23}\text{N}_5\text{O}_3\text{)},$
calc: C = 61.77, H = 6.27, N = 18.96;
found: C = 60.52, H = 6.52, N = 17.28.

¹H NMR (DMSO-d₆, 200 MHz): δ 1.1 (d, 3H), δ 1.2 (d, 3H), δ (m, 1H), δ 2.8 (m, 1H), δ 2.9-3.0 (m, 1H), δ 3.95 (d, 2H), δ 4.6 (m, 2H), δ 5.8 (d, 1H), δ 7.0-7.2 (m, 5H), δ 8.1-8.2 (br.s, 2H), δ 8.3 (s, 1H).

The starting purine was prepared as described for the starting material in Example 3 using d-amphetamine (13.3 g, 0.098 mol) and 6-chloropurine (7.73 g, 0.05 mol); yield 8.7 g (69%); mp = 190-192.5.

10 Anal (C₁₄H₁₅N₅),

calc: C = 66.38, H = 5.97, N = 27.65;

found: C = 66.20, H = 6.01, N = 27.52.

[α]_D = +87.0 (c 1.19, MeOH).

EXAMPLE 5

15 N⁶-[Cyclopentyl]-5'-deoxyadenosine

The reaction proceeded as in Example 1 with 5.0 g, 24.6 mmol of N⁶-cyclopentylpurine and 6.4 g, 24.6 mmol of the triacetate-5-deoxy sugar. The hydrolysis used 0.5 g of sodium methoxide and yielded, 20 2.6 g (33%) of extremely hygroscopic syrup.

Anal. (C₁₅N₂₁N₅O₃);

calc: C = 56.41, H = 6.63, N = 21.93;

found: C = 54.65, H = 6.45, N = 19.59.

¹H NMR (DMSO-d₆, 90 MHz): δ 1.3 (d, 3H),

25 δ 1.3-2.0 (m, 8H), δ 3.9-4.0 (m, 2H), δ 4.3-4.9 (m, 4H), δ 5.8 (d, 1H), δ 7.5-7.6 (d, 1H), δ 8.1 (s, 1H), δ 8.2 (s, 1H).

The starting purine was prepared as follows: a solution of cyclopentylamine (4.3 g, 50 mmol), triethylamine (5.05 g, 50 mmol) and 6-chloropurine (7.73 g, 50 mmol) in ethanol (250 mL) was stirred at reflux, over night. The solution cooled to 45°C and the ethanol removed in vacuo. The residue dissolved

in chloroform and washed once with water. The chloroform was evaporated in vacuo and the residue stirred into water. The precipitated solid was collected by filtration and dried at 45°C in vacuo, overnight; 5 yield 6.7 g (66%): mp = 187-191°C.

Anal (C₁₀H₁₃N₅):

calc: C = 59.09, H = 6.45, N = 34.46,
found: C = 58.75, H = 6.18, N = 34.37.

EXAMPLE 6

10 N⁶-[Cyclohexyl]-5'-deoxyadenosine

The title compound was prepared as Example 1 using 2.2 g, 10 mmol of N⁶-cyclohexylpurine and 3.1 g, 12 mmol of the triacetate-5-deoxy sugar, and purified using 10% MeOH:CHCl₃ solvent for silica gel 15 chromatography. The hydrolysis used 0.25 g of sodium methoxide and yielded; 0.61 g (18%), an extremely hygroscopic syrup.

Anal (C₁₆H₂₃N₅O₃·H₂O):

calc: C = 54.69, H = 7.17, N = 19.93;
20 found: C = 54.92, H = 7.28, N = 15.90.

¹H NMR (DMSO-d₆, 90 DMHz): δ 1.2 (d, 3H),
δ 1.1-2.0 (m, 8H), δ 3.2-3.5 (m, 2H), δ 4.5-5.3 (m,
6H), δ 5.7 (d, 1H), δ 7.3-7.5 (d, 1H), δ 8.05 (s,
1H), δ 8.15 (s, 1H).

25 The starting purine was prepared as the starting material in Example 5 using cyclohexylamine (2.0 g, 20 mmol), triethylamine (2.2 g, 20 mmol) and 6-chloropurine (3.1 g, 20 mmol); yield 3.4 g (79%): mp = 199-201°C.

30

EXAMPLE 7

(R)-N⁶[Phenylisopropyl]-5'-deoxy-5'-thiomethyl-adenosine

The title compound was prepared as in Example 11 using 5.0 g (12.9 mmol) (R)-N⁶-[phenylisopropyl]

adenosine, 13.2 g (65 mmol) tri-n-butyl phosphine, and 6.1 g (65 mmol) dimethyldisulfide, yield 28%.
Anal. Calcd. for: C₂₀H₂₅N₅O₃S
calc: C, 57.81; H, 6.06; N, 16.86; S, 7.72;
5 Found: C, 57.71; H, 6.28; N, 16.49; S, 8.07.

EXAMPLE 8

(S)-N⁶-[Phenylisopropyl]-5'-deoxy-5'-thiomethyl-adenosine

The intermediate (S)-N⁶-[phenylisopropyl]-adenosine-2',3'-isopropylidene was prepared as in Example 12 using (S)-N⁶-[phenylisopropyl]-adenosine (8.4 g, 22 mmol), dimethoxypropane (25 ml) and Hampton's reagent (8.5 g, 25 mmol). [see J. Am. Chem. Soc. 83, 3640 (1961)]. Yield 61%; this compound (13.3 mmol) was then treated with thionylchloride (1.8 g, 15 mmol) in the manner described in Example 12; this compound (3.7 g, 8.3 mmol) was then treated with lithium methyl mercaptan (2.3 g, 42 mmol) (yield 53%), and deprotected as in Example 12 to give 20 81% final product, mp 23-24°C.

Anal. Calcd. for: C₂₀H₂₅N₅O₃S

calc: C, 57.81; H, 6.06; N, 16.86; S, 7.72;

Found: C, 56.81; H, 5.77; N, 15.83; S, 8.74.

1 NMR (DMSO-d₆, 90 MHz): δ 1.2 (d, 3H), δ 2.0 (s, 2H), δ 2.6-3.0 (m, 4H), δ 4.1 (m, 2H), δ 4.6 (m, 2H), δ 5.2 (d, 1H), δ 5.4 (d, 1H), δ 5.85 (d, 1H), δ 7.0-7.3 (m, 5H), δ 7.6 (br.d, 1H), δ 8.15 (s, 1H), δ (s, 1H).

EXAMPLE 9

30 N⁶-[Cyclohexyl]-5'-deoxy-5'-thiomethyladenosine
N⁶-[Cyclohexyl]-5'-deoxy-5'-thiomethyladenosine was prepared in a manner analogous to Example 12 using

5.0 g N^6 -[cyclohexyl]-5'-deoxy-5'-chloroadenosine-2',3'-isopropylidene and lithium methyl mercaptide (2.7 g) to give the 5'-thiomethyl-isopropylidene intermediate, followed by deprotection to give the 5 final product, yield 58%.

Anal. Calcd. for: $C_{17}H_{25}N_5O_3S$

calc: C, 53.81; H, 6.64; N, 18.46; S, 8.48;

Found: C, 53.00; H, 6.66; N, 18.19; S, 6.88;
water 2.35.

10 1H NMR (DMSO- d_6 , 90 MHz): δ 1.1-2.0 (m, 10H),
 δ 2.0 (s, 3H), δ 2.8 (m, 1H), δ 3.8-4.3 (m,
4H), δ 4.65 (m, 1H), δ 5.1-5.4 (m, 2H), δ 5.85 (d,
1H), δ 7.4 (br.d, 1H), δ 8.1 (s, 1H), δ 8.25 (s, 1H).

N^6 -[Cyclohexyl]-5'-deoxy-5'-chloroadenosine-2',

15 3'-isopropylidene was synthesized as in Example 12
utilizing 12.5 g. N^6 -[Cyclohexyl]adenosine,
dimethoxy propane 80 ml and Hampton's catalyst 15.2 g
to give the isopropylidene, followed by treatment with
5.3 g thionyl chloride. The compound was isolated as
20 the hydrochloride salt.

EXAMPLE 10

N^6 -[Cyclopentyl]-5'-deoxy-5'-thiomethyladenosine

The title compound was prepared using N^6 -(cyclopentyl)-5'-deoxy-5'-chloroadenosine-2',3'-isopropyl-

25 idene (5.7 g, 13.2 mmol) and lithium methyl mercaptide (4.3 g, 80 mmol) as in Example 12, yield 74%. This was
deprotected as in Example 12 to give N^6 -cyclopentyl]-
5'-deoxy-5'-thiomethyl adenosine, yield 69%.

Anal. Calcd. for: $C_{16}H_{23}N_5O_3S$

30 calc: C, 52.59; H, 6.34; N, 19.16; S, 8.77;

Found: C, 51.67; H, 6.67; N, 17.25; S, 8.59.

1H NMR (DMSO- d_6 , 90 MHz): δ 1.4-2.1 (m, 8H),
 δ 2.0 (s, 3H), δ 2.8 (m, 2H), δ 3.9-4.2 (m,

2H), δ 4.5-4.8 (m, 3H), δ 5.85 (d, 1H), δ 7.6 (br.d, 1H), δ 8.2 (s, 1H), δ 8.3 (s, 1H).

The 5'-deoxy-5'-chloroisopropylidene intermediate was synthesized as in Example 12 using

5 N^6 -[cyclopentyl]-adenosine (5 g, 15 mmol), dimethoxy propane (18 ml) and Hampton's reagent (6.3 g, 19 mmol), yield 86%; following this treatment with 4.1 g (10 mmol) thionyl chloride isolated the intermediate as the hydrochloride salt (yield 49%).

10

EXAMPLE 11

 N^6 -[2,2-Diphenyl]-5'-deoxy-5'-thiomethyladenosine

N_6 -(2,2-diphenylethyl)adenosine (4.7 g, 10.5 mmol) and tri-n-butylphosphine (10.8 g, 53 mmol) in DMF (20 mL) was stirred, under N_2 , at room 15 temperature for 48 hours. The reaction mixture was diluted with water (20 mL) and the solvents were removed by distillation (<90°C, 1 mmHg). The glossy black residue was purified by silica gel chromatography eluting with ethyl acetate. The major 20 fraction was isolated by evaporation of the solvent to give a white foam; yield 1.4 g (28%), mp 70-90°C.

Anal. Calcd. for: $C_{25}H_{27}N_5O_3S$

calc: C, 62.87; H, 5.70; N, 14.66; S, 6.71;

Found: C, 62.32; H, 5.73; N, 14.25; S, 6.72.

25 1H NMR (DMSO-d₆, 200 MHz): δ 2.0 (s, 3H), δ 2.8 (m, 2H), δ 4.0-4.2 (m, 4H), δ 4.6 (m, 1H), δ 4.7 (m, 1H), δ 5.3 (d, 1H), δ 5.5 (d, 1H), δ 5.9 (d, 1H), δ 7.1-7.4 (m, 10H), δ 7.8 (br.s, 1H), δ 8.3 (br.s, 2H).

30 N^6 -(2,2-diphenylethyl)adenosine was prepared as follows: In 250 ml of absolute ethanol was refluxed 14.3 g 6-chloropurine riboside, 9.8 g (2,2-diphenyl) ethylamine and 5.0 g of triethylamine for 18 hours. The solution was cooled to 8°C and solids collected by

filtration. The solids were partitioned between 100 ml methylene chloride and 100 ml water. The organics were dried over magnesium sulfate and the solvent removed in vacuo to give a foam, dried on high 5 vacuum for four hours, mp 88-101°C. Anal. Calcd. for:



calc: C, 63.14; H, 5.74; N, 15.34;

Found: C, 62.82; H, 5.71; N, 15.10.

EXAMPLE 12

10 N⁶-[1-Indanyl]-5'-deoxy-5'-thiomethyladenosine
A mixture of N⁶-[1-indanyl]-5'-deoxy-5'-chloro-2',3'-isopropylidene adenosine (3.3 g, 6.9 mmol) and lithium methyl mercaptide (2.2 g, 40 mmol) in THF (200 mL) was heated to reflux 15 and stirred 72 hours. The reaction cooled to room temperature and quenched with water (100 mL). The THF was removed in vacuo and the solution extracted with methylene chloride (100 mL). The organics were dried over MgSO₄ and the solvent was 20 removed in vacuo to give a foam. The foam, the 5'-SMe-5'-deoxy-isopropylidene derivative, was dried on high vacuum at room temperature, 4 hours; yield 1.2 g (39%). This material was stirred into 50% aqueous formic acid (100 mL) and stirred at 50°C for 25 four hours. The formic acid/water was removed in vacuo and the residue coevaporated to dryness with methanol, to give a foam. The foam was purified by silica gel chromatography eluting with acetone, and the major component was isolated by evaporation of the 30 solvent. The resultant hygroscopic yellow foam was dried on high vacuum at room temperature; yield 1.3 g (81%).

Anal. Calcd. for: C₂₀H₂₃N₅O₃SH₂O

calc: C, 55.67; H, 5.61; N, 16.23; S, 7.41;

Found: C, 56.41; H, 5.91; N, 15.17; S, 5.74.

¹H NMR (DMSO-d₆, 200 MHz): δ 2.0 (s, 3H),

5 δ 2.8-3.1 (m, 5H), δ 4.0-4.2 (m, 2H), δ 4.5 (m, 1H), δ 4.8 (m, 1H), δ 5.3 (d, 1H), δ 5.5 (d, 1H), δ 5.9 (d, 1H), δ 5.9-6.0 (br.s, 1H), δ 7.1-7.3 (m, 4H), δ 8.1 (br.d, 1H), δ 8.3 (br.s, 1H), δ 8.5 (s, 1H).

10 The starting material was prepared as follows: A solution of dimethoxy propane (30 mL), N⁶-(1-indanyl)-adenosine (9.0 g, 23.5 mmol) and Hampton's reagent (bis-p-nitrophenylphosphate hydrate), [J. Am. Chem. Soc. 83, 3640 (1961)], (9.6 g, 28 mmol) in acetone (150 mL) was stirred at room temperature, with exclusion of moisture, overnight. The reaction was quenched with ~5% NaHCO₃ solution (125 mL) and the solution stirred for one half hour. The acetone was removed in vacuo and the residue dissolved in methanol. The methanolic solution was poured through a Dowex 1 x 8 (NH₄⁺HC₃O⁻) column, eluted with methanol (300 mL). The methanol was removed in vacuo to give the isopropylidene, yield 6.4 g (65%). The isopropylidene (6.1 g, 14.4 mmol) was placed in THF (150 mL) and treated with thionyl chloride (2.4 g, 20 mmol). The solution was warmed to reflux for one hour then cooled to room temperature and stirred, overnight. The THF was removed in vacuo at 40°C and the residue dissolved in methylene chloride (150 mL). The solution was washed with water (2 x 100 mL) and dried over MgSO₄. The solvent was then removed in vacuo to give a yellow foam, the N⁶-(indanyl)-5'-chloro-5'-deoxy-isopropylidene adenosine 0.8 HCl, yield 5.5 g (81%).

35 N⁶-(1-Indanyl)adenosine was in turn prepared as follows: Four grams 6-chloropurine riboside,

2.32 g 1-aminoindane and 2.11 g of triethylamine were refluxed in 100 ml of absolute ethanol under nitrogen for 20 hours. Volatiles were evaporated to dryness. Residue was dissolved in 20 ml 2-propanol and diluted 5 with 200 ml H₂O. Clear aqueous solution was decanted and residual oily material washed with cold water. Coevaporation with ethanol several times gave solid material. Crystallization from CHCl₃/2-propanol (10:1) and hexane afforded 3.0 g (56.2%) N⁶-(1-indanyl)adenosine having a melting point of 120-122°C (foam).

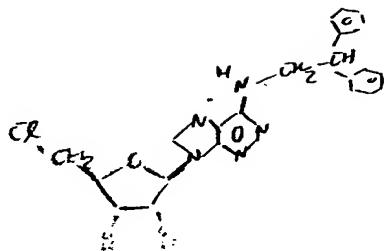
Anal. Calcd. for: C₁₉H₂₁N₅O₄

calc: C, 59.52; H, 5.52; N, 18.26;

Found: C, 59.37; H, 5.48; N, 18.00.

15

EXAMPLE 13

N⁶-[2,2-Diphenylethyl]-5'-deoxy-5'-chloroadenosine

The intermediate N⁶-[2,2-diphenylethyl]-5'-deoxy-5'-chloroadenosine-2',3'-isopropylidene was synthesized as in Example 14 from N⁶-[2,2-diphenylethyl]adenosine (2.2 g, 4.7 mmol), dimethoxypropane (8 ml) and Hampton's reagent¹ (1.9 g, 5.6 mmol), (yield 1.8 g, 78%), followed by treatment with 1.5 equivalents of thionylchloride (yield-59%). The isopropylidene was hydrolyzed to the final compound as 25 in Example 14 (yield 36%) mp 180-183°C.

Analysis as (C₂₄H₂₄ClN₅O₃)

Calc'd: C, 61.87; H, 5.19; N, 15.03; Cl, 7.61;

Found: C, 61.48; H, 5.19; N, 14.62; Cl, 8.51.

¹H NMR (DMSO-d₆, 200 MHz): δ 3.8-3.9 (m, 2H), 30 δ 4.0-4.2 (m, 3H), δ 4.6 (m, 2H), δ 4.7 (d of d, 1H), δ 5.4 (d, 1H), δ 5.55 (d, 1H), δ 5.9 (d,

¹ J. Am. Chem. Soc., 83, 3640 (1961)

1H), δ 7.1-7.3 (m, 10H), δ 7.8 (br.s, 1H),
δ 8.2 (s, 2H).

The starting N^6 -(2,2-diphenylethyl)adenosine was prepared as follows:

5 In 250 ml of absolute ethanol was refluxed 14.3 g 6-chloropurine riboside, 9.8 g (2,2-diphenyl)ethylamine and 5.0 g of triethylamine for 18 hours. The solution cooled to 8°C and solids collected by filtration. The solids were partitioned between
10 100 ml methylene chloride and 100 ml water. The organics was dried over magnesium sulfate and the solvent removed in vacuo to give a foam dried on high vacuum for four hours. mp 88-101°C.
Anal (C₂₄H₂₅N₅O₇·0.5H₂O)
15 Calc'd: C, 63.14; H, 5.74; N, 15.34;
Found: C, 62.82; H, 5.71; N, 15.10.

EXAMPLE 14

N^6 -[1-Indanyl]-5'-deoxy-5'-chloroadenosine

A solution of dimethoxy propane (30 ml), N^6 -(1-indanyl)adenosine (9.0 g, 23.5 mmol) and Hampton's reagent¹ (bis-p-nitrophenylphosphate hydrate) (9.6 g, 28 mmol) in acetone (150 ml) was stirred at room temperature, with exclusion of moisture, overnight. The reaction was quenched with ~5% NaHCO₃ solution
25 (125 mL) and the solution stirred for one half hour. The acetone was removed in vacuo and the residue dissolved in methanol. The methanolic solution was poured through a Dowex 1 x 8 (NH₄⁺HCO₃⁻) column, eluted with methanol (300 mL). The methanol was
30 removed in vacuo to give the isopropylidene, yield 6.4 g (65%). The isopropylidene (6.1 g, 14.4 mmol)

was placed in THF (150 mL) and treated with thionyl chloride (2.4 g, 20 mmol). The solution was warmed to reflux for one hour then cooled to room temperature and stirred, overnight. The THF was removed in vacuo at 40°C and the residue dissolved in methylene chloride (150 mL). The solution was washed with water (2 x 100 mL) and dried over MgSO₄. The solvent was then removed in vacuo to give a yellow foam, the 5'-chloro-5'-acoxvisopropylidene-0.8HCl, yield 5.5 g (81%). The protected 5'-chloro compound (2.0 g, 4.2 mmol) was then dissolved in 50% aqueous formic acid (110 mL) and the solution was warmed to 60°C for four hours. The formic acid/water was removed in vacuo and the residue coevaporated to dryness with methanol to give a white foam. This foam was purified by silica gel chromatography eluting with acetone. The major component was isolated by evaporation of acetone to give a very hygroscopic white solid, dried in vacuo at room temperature, overnight; yield 0.85 g (50%).

Anal (C₁₉H₂₀ClN₅O₃·H₂O),

Calc'd: C, 54.35; H, 5.04; N, 16.68; Cl, 8.44;

Found: C, 54.52; H, 5.40; N, 15.47; Cl, 8.54.

¹H NMR (DMSO-d₆, 100 MHz): δ 1.0-1.5 (m, 2H),

δ 2.8-3.1 (m, 2H), δ 3.9 (d of d, 2H),

δ 4.0-4.3 (m, 2H), δ 4.8 (d of d, 1H),

δ 5.5 (d, 1H), δ 5.6 (d, 1H), δ 5.95 (d, 1H),

δ 7.1-7.3 (m, 4H), δ 8.2 (br.d, 1H), δ 8.3 (s, 1H), δ 8.35 (s, 1H).

The starting N(6)-(1-Indanyl)adenosine was prepared as follows:

Four grams 6-chloropurine riboside, 2.32 g 1-aminoindane and 2.11 g of triethylamine were refluxed in 100 ml of absolute ethanol under nitrogen for 20 hours. Volatiles were removed. The residue was dissolved in 20 ml 2-propanol and diluted with 200 ml H₂O. Clear aqueous solution was decanted and

residual oily material washed with cold water. Coevaporation with ethanol several times gave solid material. Crystallization from CHCl_3 /2-propanol (10:1) and hexane afforded 3.0 g (56.2%) $\text{N(6)-(1-5 indanyl)adenosine}$ having a melting point of 120-122°C (foam).

Anal ($\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}_4$)

Calc'd: C, 59.52; H, 5.52; N, 18.26;

Found: C, 59.37; H, 5.48; N, 18.00.

10

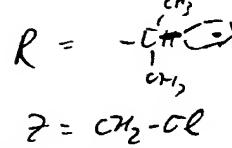
EXAMPLE 15

(R)-N⁶-[Phenylisopropyl]-5'-deoxy-5'-chloro-adenosine

S. Form
4m 85
16

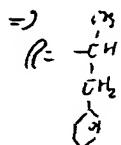
A solution of thionylchloride (8.3 g, 70 mmol) in HMPA (25 mL) was treated with (R)-N⁶-(phenyl-isopropyl)adenosine (5 g, 13 mmol) and the mixture 15 stirred at room temperature, overnight. The reaction was quenched with water (80 mL) and neutralized with ammonium hydroxide. The gum that formed was separated from the solution, and washed with water (30 mL). The gum was dissolved in ethanol and 20 evaporation in vacuo to give a foam. The compound was dissolved in ethanol (20 mL) and passed through silica gel, eluted with ethanol (100 mL). The ethanol evaporated in vacuo. The residue was dissolved in methylene chloride and dried over MgSO_4 . 25 evaporated in vacuo to give a yellow foam; yield 1.65 g (31%); mp = 83-86. Anal ($\text{C}_{19}\text{H}_{22}\text{ClN}_5\text{O}_3$) Calc'd: C, 56.50; H, 5.49; N, 17.34; Cl, 8.78; Found: C, 56.34; H, 5.60; N, 17.37; Cl, 8.41.

EXAMPLE 16



R-Form

Amid 1

(S)-N⁶-[Phenylisopropyl]-5'-deoxy-5'-chloroadenosine

The title compound was synthesized as in Example 15 using (S)-N⁶-(phenylisopropyl)adenosine (15.4 g, 40 mmol), HMPA (80 mL) and thionyl chloride (25.5 g, 215 mmol); yield 11% mp 75-110°. Analysis for (C₁₉H₂₂ClN₅O₃)

Calc'd: C, 56.60; H, 5.49; N, 17.34; Cl, 8.78;
 Found: C, 56.14; H, 5.42; N, 16.99; Cl, 8.77.

10 ¹H NMR (DMSO-d₆, 90 MHz): δ 1.2 (d, 3H),
 δ 2.7-3.2 (m, 2H), δ 3.9-4.0 (m, 2H),
 δ 4.05-4.4 (m, 2H), δ 4.8 (d of d, 2H), δ 5.5 (d, 1H), δ 5.6 (d, 1H), δ 6.0 (d, 1H), δ 7.1-7.4 (m, 5H), δ 7.7 (br.d, 1H), δ 8.2 (s, 1H), δ 8.3 (s, 1H).

15

EXAMPLE 17

N⁶-[Cyclohexyl]-5'-deoxy-5'-chloro-adenosine

N⁶-[Cyclohexyl]-5'-deoxy-5'-chloro-adenosine was synthesized as in Example 14 utilizing 12.5 g, N⁶-[cyclohexyl]adenosine, dimethoxypropane 80 mL and 20 Hampton's catalyst 15.2 g to give the isopropylidene, followed by treatment with 5.3 g, thionyl chloride and deprotection. Yield 40% mp 65-85°. Analysis for (C₁₆H₂₂N₅O₃Cl)

Calc'd: C, 52.24; H, 6.03; N, 19.04; Cl, 9.64;
 25 Found: C, 51.20; H, 5.72; N, 17.26; Cl, 13.32.
¹H NMR (DMSO-d₆, 90 MHz): δ 1.1-2.0 (m, 11H),
 δ 3.8-4.0 (m, 2H), δ 4.0-4.3 (m, 2H), δ 4.75 (d of d, 1H), δ 5.45 (d, 1H), δ 5.55 (d, 1H), δ 5.9 (d, 1H), δ 7.5 (br.d, 1H), δ 8.2 (s, 1H), δ 8.3 (s, 1H).

→ C₃-C₆ -
 cyclohexylidene
 and γ=H

50% O. scheme

EXAMPLE 18

N⁶-[Cyclopentyl]-5'-deoxy-5'-chloroadenosine

The isopropylidene intermediate was synthesized as in Example 14 using N⁶-[cyclopentyl]-adenosine 5 (5 g, 15 mmol), dimethoxyp propane (18 ml) and Hampton's reagent (6.3 g, 19 mmol) yield 86%. The 5'-chloro-5'-deoxy isopropylidene analog was synthesized as in Example 14 using 4.1 g (10 mmol) N⁶-[cyclopentyl]-adenosine-2'-3'-isopropylidene and 1.3 g (10 mmol) 10 thionyl choride and was isolated as the hydrochloride salt (yield 49%). This was hydrolyzed as in Example 14 to give N⁶-[cyclopentyl]-5'-deoxy-5'-chloroadenosine. Mp ~70°C. Anal (C₁₅H₂₀ClN₅O₃).
Calc'd: C, 50.92; H, 5.70; N, 19.80; Cl, 10.02.
15 Found: C, 50.54, H, 5.84; N, 19.12; Cl, 10.64.
H NMR (DMSO-d₆, 90 MHz): δ 1.4-2.1 (m, 9H),
δ 3.85 (m, 3H), δ 4.2 (m, 2H), δ 4.6 (m, 2H),
δ 5.9 (d, 1H), δ 8.4 (s, 1H), δ (s, 1H),
δ 8.6 (s, 1H), δ 9.5 (s, 1H).

20

EXAMPLE 19

N⁶-1-Tetralinyl-5'-deoxyadenosine

Six chloropurine (7.7 g, 50 mmol), triethyl amine (5.1 g, 50 mmol) and 1-aminotetralin (7.4 g, 50 mmol) were stirred at reflux in 150 ml of ethanol, overnight. 25 The solution was cooled to 0°C and filtered free of precipitate. The precipitate washed with 50 ml of cold (0°C) ethanol and dried at 60°C in vacuo for four hours to give 4.2 g (32%) of a white solid, mp 232.5-234°C.
30 Anal C₁₅H₁₅N₅
calc: C, 67.90; H, 5.70; N, 26.40
Found: C, 67.99; H, 5.62; N, 26.41

The adenine (5.3 g, 20 mmol) and 5'-deoxy ribose triacetate (6.5 g, 25 mmol) were melted and stirred at 190°C. To the melt was added one micro drop of concentrated sulfuric acid and the acetic acid formed 5 was removed in a gentle stream of nitrogen. The solution was stirred for two hours before cooling to room temperature. The glassy residue was broken up in 20 ml of ethyl acetate in an ultrasonic bath. The solution was then purified by chromatography to give 10 after evaporation of the solvent 4.7 g of a light brown foam identified herein after as the compound D in Example 22. The foam (4.0 g, 8.6 mmol) was then dissolved in 100 ml of methanol and sodium methoxide (0.5 g, 8.6 mmol) added. The solution was stirred at 15 room temperature for four hours. The reaction was neutralized with Dowex 50 x 8 (H⁺ form) to pH 7 and the resin removed by filtration. The filtrate was evaporated in vacuo and the residue stirred into 4.0 ml of acetone and the solid collected by filtration and dried at 40°C overnight, to give 1.95 g 20 (30%) of a hydroscopic white solid, mp 159-162°C.

Anal C₂₀H₂₃N₅O₃

calc: C, 62.98; H, 6.08; N, 18.36

Found: C, 62.87, H, 6.21; N, 18.18

25

EXAMPLE 20

N⁶- α -Naphthylmethyl-5'-deoxyadenosine

Six chloropurine (7.6 g, 50 mmol), triethyl amine (5.1 g, 50 mmol) and α -naphthylmethyl amine (7.9 g, 50 mmol) were stirred, at reflux, in 150 ml of 30 ethanol, overnight. The solution was cooled to 0°C and filtered free of precipitate and the precipitated solid washed with cold ethanol. The solid was dried at room temperature in vacuo overnight to give 10.6 g (77%) of a white solid, mp 250-252.5°C.

The adenine (5.5 g, 20 mmol) and 5' deoxy ribose (6.5 g, 25 mmol) were melted and stirred at 200-220°C. To the melt was added one micro drop of concentrated sulfuric acid and the acetic acid formed 5 was removed in a gentle stream of nitrogen. The solution was stirred for six hours before cooling to room temperature. The glassy residue was broken up in 30 ml of ethyl acetate in an ultrasonic bath. The solution was then purified by chromatography to give 10 after evaporation of the solvent 3.9 g of a white foam that is the compound identified as 21 hereinafter. The foam (3.0 g, 6.3 mmol) was then dissolved in 100 ml of methanol and sodium methoxide (0.4 g, 6.3 mmol) added. The solution was stirred at 15°C room temperature for four hours. The reaction was neutralized with Dowex 50 x 8 (H⁺ form to pH 7 and the resin removed by filtration. The filtrate was evaporated in vacuo and the residue recrystallized from 30 ml of ethanol. The solid was collected by 20 filtration and dried at 40°C in vacuo, overnight, to give 1.9 g (31%) of a hygroscopic light brown solid, mp 124-128°C.

EXAMPLE 21

N⁶- α -Naphthylmethyl-2',3'-di-O-acetyl-5'-deoxyadenosine

25 Compound 21 from Example 20 was analyzed to give the product N⁶-(α -naphthyl)methyl-5'-deoxy-2',3'-diacetyl adenosine 3.9 g (41%), mp 70-78°C. Anal C₂₅H₂₅N₅O₅ Calc'd: C, 63.15; H, 5.30; N, 14.73 Found: C, 62.91; H, 5.50; N, 14.57

EXAMPLE 22

N⁶-1-Tetralinyl-2',3'-di-O-acetyl-5'-deoxyadenosine

Compound D from Example 19 was analyzed to give the product N⁶-(1-tetralinyl)-5'-deoxy-2',3'-diacetyl-5 adenosine 4.7 g (51%), mp 70-72°C.

Anal C₂₄H₂₇N₅O₅

calc: C, 61.92; H, 5.85; N, 15.05

Found: C, 61.98; H, 6.05; N, 14.96

EXAMPLE 23

10 (R)-N⁶(1-Indanyl)-5'-deoxy-5'-chloroadenosine

A solution of dimethoxy propane (25 ml), N⁶-(R)-1-indanyl-adenosine (9.6 g, 25 mmol) and bis-p-nitrophenyl-phosphate hydrate (9.5 g, 28 mmol) in acetone (200 ml) was stirred at room 15 temperature, overnight. The solution was quenched with water (150 ml) and the acetone evaporated in vacuo. The aqueous solution was extracted with methylene chloride (2 x 150 ml) and the organic solution washed with water (100 ml) and then saturated salt 20 solution (100 ml) and then saturated salt solution (100 ml). The organic solution was dried over magnesium sulfate and the solvent evaporated in vacuo. The residue was dissolved in methanol (75 ml) and passed through a short column of Dowex 1 x 8 (sodium 25 bicarbonate form) ion exchange resin. The column washed with methanol (580 ml total). The methanol was then evaporated in vacuo to give the isopropylidene analog 8.8 g (83%). The isopropylidene (7.5 g, 17.7 mmol) was placed in THF (100 ml), treated with thionyl 30 chloride (3.2 g, 26.5 mmol) and stirred at room temperature overnight. The solution was evaporated in vacuo to dryness and the residue dissolved in methylene chloride (100 ml). The organic solution

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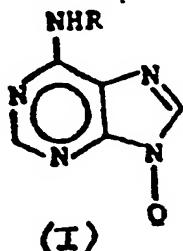
was washed with water (100 ml), saturated salt solution (100 ml) and dried with magnesium sulfate. The solvents were evaporated in vacuo and the residue purified by chromatography to give, after evaporation of solvent from the major RI active fraction, 5.5 g (71%) of a light yellow foam. The foam (4.8 g, 10.9 mmol) was then dissolved in 50% formic acid (100 ml) and stirred at 50°C for 4.5 hours. The solution was evaporated in vacuo to dryness and the residue purified by chromatography. This gave, after evaporation of solvent from the major RI active fraction, 2.5 g (57%) of a white foam, mp 94-97°C.

Anal (C₁₉H₂₀ClN₅O₃)
calc: C, 56.79; H, 5.02; N, 17.43
15 Found: C, 56.60; H, 5.18, N, 17.60

CLAIMS (for BE, CH, DE, FR, GB, IT, LI, LU, NL, SE)

1. A compound of the following general formula

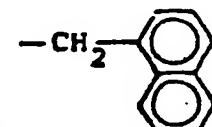
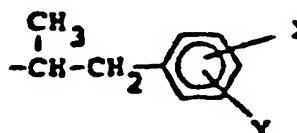
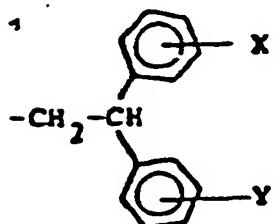
(I)



5

or a pharmaceutically acceptable acid addition salt
10 thereof, wherein:

R is cycloalkyl having from three to eleven
ring members or R is one of the following groups of the
formulae



20

(Ia)

(Ib)

(Ic)

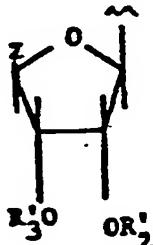
(Ie)

in which

n is one, two, or three;

25 X and Y are each, independently, H, lower alkyl,
hydroxy, lower alkoxy, benzyloxy, nitro, amino or
halogen; and

Q is of the formula:



30

in which

35 Z is CH₃, CH₂Hal in which Hal stands for a halogen
atom or CH₂SCH₃; and

5 R_2' or R_3' are each, independently, H, lower alkyl, lower alkanoyl, benzoyl, benzoyl substituted by lower alkyl, lower alkoxy, or halogen, or when taken together are lower alkylidene where the hydroxy groups are free or lower alkanoyl or benzoyl esters thereof.

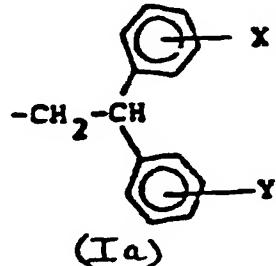
2. A compound according to Claim 1, wherein Z is $-\text{CH}_3$.

10 3. A compound according to Claim 1, wherein Z is $-\text{CH}_2\text{SCH}_3$.

4. A compound according to Claim 1, wherein Z is $-\text{CH}_2\text{Hal}$ in which Hal is a halogen atom, preferably chlorine.

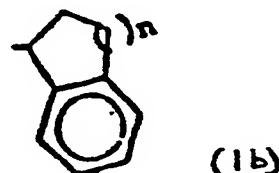
15 5. A compound according to Claim 2, 3 or 4, wherein R is of the formula (Ia) :

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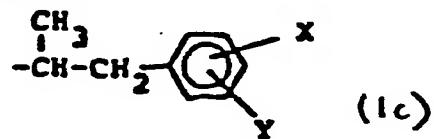
6. A compound according to Claim 2, 3 or 4, 25 wherein R is of the formula (Ib)

30



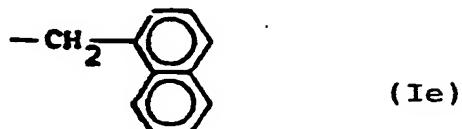
7. A compound according to Claim 2, 3 or 4, wherein R is of the formula (Ic) :

35



8. A compound according to Claim 2, 3 or 4,
wherein R is of the formula (Ie)

5



9. A compound according to Claim 2, 3 or 4,
10 wherein R is a cycloalkyl radical having from three to
eleven ring members, preferably from five to seven ring
members.

10. A compound according to Claim 5, 6 or 7,
wherein X and Y are hydrogen.

15 11. A compound according to Claim 10, wherein Q
is 5'-deoxy- β -D-ribose and OR₂' and OR₃' are hydroxy or
acetyl esters thereof.

12. A compound according to Claim 11 when
appendant to Claims 2 and 5, and being
20 5'-deoxy-N⁶-(2,2-diphenylethyl)adenosine.

13. A compound according to Claim 11 when
appendant to Claims 2 and 6, and being chosen from :
5'-deoxy-N⁶-(1-indanyl)adenosine;
N⁶-1-tetralinyl-5'-deoxyadenosine; and
25 N⁶-1-tetralinyl-5'-deoxyadenosine-2',3'-di-O-acetyl.

14. A compound according to Claim 11 when
appendant to Claims 2 and 7, and being chosen from :
(R)-5'-deoxy-N⁶-(1-methyl-2-phenylethyl) adenosine; and
(S)-5'-deoxy-N⁶-(1-methyl-2-phenylethyl)adenosine.

30 15. A compound according to Claim 8 when appen-
dant to Claim 2, and being chosen from:
N⁶- α -naphthylmethyl-5'-deoxyadenosine; and
N⁶- α -naphthylmethyl-3'-deoxyadenosine-2',3'-di-O-acetyl.

16. A compound according to Claim 9 when appendant to Claim 2, wherein Q is 5'-deoxy- β -D-ribose and OR₂' and OR₃' are each hydroxy or acetyl esters thereof.

5 17. A compound according to Claim 16, and being 5'-deoxy-N⁶-(cyclopentyl)adenosine.

18. A compound according to Claim 10, when appendant to Claim 3, wherein R₂' and R₃' are each independently hydrogen, acetyl, benzoyl or, when taken 10 together, isopropylidene.

19. A compound according to Claim 18, when further appendant to Claim 5, and being : 5'-deoxy-5'-methylthio-N⁶-(2,2-diphenylethyl)adenosine.

20. A compound according to Claim 18 when further 15 appendant to Claim 6, and being : 5'-deoxy-5'-methylthio-N⁶-(1-indanyl)adenosine.

21. A compound according to Claim 18 when further appendant to Claim 7, and being chosen from : (R)-5'-deoxy-5'-methylthio-N⁶-(1-methyl-2-phenylethyl)- 20 adenosine; and (S)-5'-deoxy-5'-methylthio-N⁶-(1-methyl-2-phenylethyl) adenosine;

22. A compound according to Claim 9 when appendant to Claim 3, wherein R₂' and R₃' are each independently hydrogen, acetyl, benzoyl or, when taken together, isopropylidene.

23. A compound according to Claim 22, wherein R₂' and R₃' are hydrogen.

24. A compound according to Claim 23 and being : 30 5'-deoxy-5'-methylthio-N⁶-(cyclopentyl)adenosine.

25. A compound according to Claim 10 when appendant to Claim 4, wherein R₂' and R₃' are each independently hydrogen, acetyl or benzoyl, or R₂' and R₃' when taken together are isopropylidene.

35 26. A compound according to Claim 25 when further appendant to Claim 5 and being :

5'-deoxy-5'-chloro-N⁶-(2,2-diphenylethyl)adenosine.

27. A compound according to Claim 25 when further appendant to Claim 6, and being chosen from:

5'-deoxy-5'-chloro-N⁶-(1-indanyl)adenosine; and

5 (R)-N-6-(1-indanyl)-5'-deoxy-5'-chloro-adenosine.

28. A compound according to Claim 25 when further appendant to Claim 7, and being chosen from :

(R)-5'-deoxy-5'-chloro-N⁶-(1-methyl-2-phenylethyl)-adenosine; and

) (S)-5'-deoxy-5'-chloro-N⁶-(1-methyl-2-phenylethyl)-adenosine

29. A compound according to Claim 9 when appendant to Claim 4, wherein R₂' and R₃' are each independently hydrogen, acetyl, benzoyl or when taken together an isopropylidene.

30. A compound according to Claim 29, wherein R₂' and R₃' are each hydrogen.

31. A compound according to Claim 30 and being :
5'-deoxy-5'-chloro-N⁶-(cyclopentyl)adenosine.

) 32. A pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in any preceding claim together with a pharmaceutically acceptable carrier or diluent.

33. For use in a method of treating psychoses in a mammal suffering therefrom, a compound as claimed in any one of Claims 1 to 31, preferably in unit dosage form. *17. RQ*

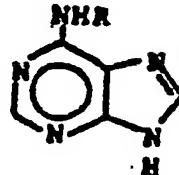
34. For use in a method of treating hypertension in a mammal suffering therefrom a compound as claimed in any one of Claims 1 to 31, preferably in unit dosage form.

35. For use in a method of treating pain in a mammal suffering therefrom, a compound as claimed in any one of Claims 1 to 31, preferably in unit dosage form.

36. A process for the preparation of a compound

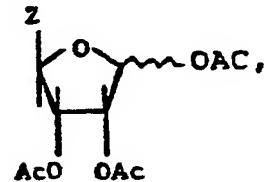
as claimed in Claim 1, which comprises reacting a
N-6-substituted purine of the formula

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wherein R is as defined in claim 1, with a compound of
the formula



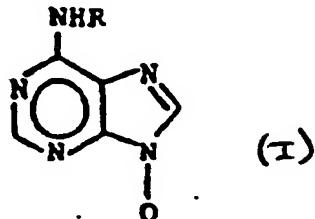
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wherein Z is as defined in Claim 1, at elevated
temperatures from about one to about 12 hours and,
if desired, converting the resulting free base to a
pharmaceutically acceptable acid addition salt thereof.

20

CLAIMS (for AT)

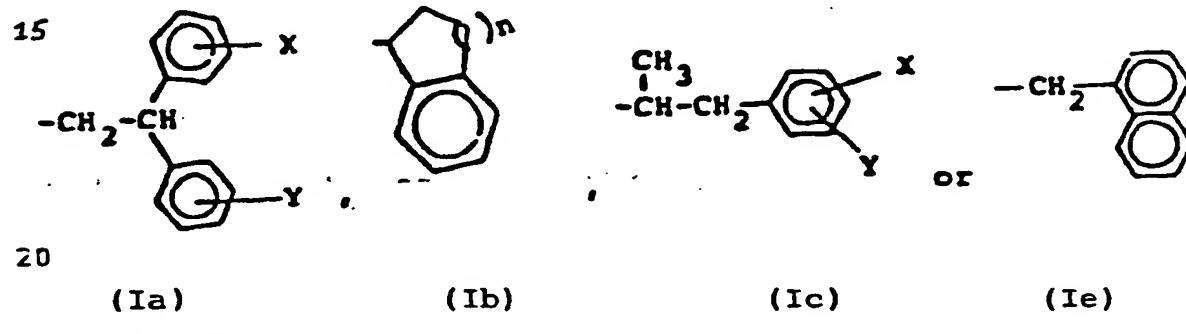
1. A process for preparing a compound of the following general formula (I)



or a pharmaceutically acceptable acid addition salt thereof, wherein

10

R is cycloalkyl having from three to eleven ring members or R is one of the following groups of the formulae



(18)

(1b)

(Ic)

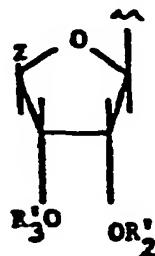
(Ie)

IN WHICH

n is one, two, or three;

25 X and Y are each, independently, H, lower alkyl, hydroxy, lower alkoxy, benzyloxy, nitro, amino or halogen; and

Q is of the formula:



in which

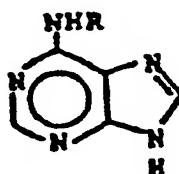
35 z is CH_3 , CH_2Hal in which Hal stands for a halogen

atom or CH_2SCH_3 ; and

5 R_2' or R_3' are each, independently, H, lower alkyl, lower alkanoyl, benzoyl, benzoyl substituted by lower alkyl, lower alkoxy, or halogen or when taken together are lower alkylidene where the hydroxy groups are free or lower alkanoyl or benzoyl esters thereof;

which process comprises reacting an N-6-substituted purine of the formula

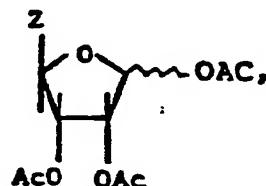
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wherein R is as defined above, with a compound of the formula

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25 wherein Z is as defined above, at elevated temperatures for from about one to about 12 hours and, if desired, converting the resulting free base to a pharmaceutically acceptable acid addition salt thereof.

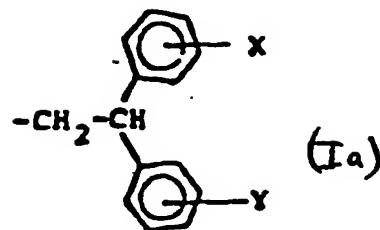
2. A process according to Claim 1, wherein Z is $-\text{CH}_3$.

30 3. A process according to Claim 1, wherein Z is $-\text{CH}_2\text{SCH}_3$.

4. A process according to Claim 1, wherein Z is $-\text{CH}_2\text{Hal}$ in which Hal is a halogen atom, preferably chlorine.

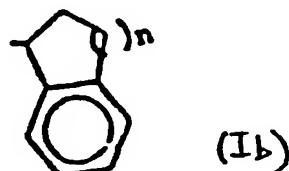
35 5. A process according to Claim 2, 3 or 4, wherein R is of the formula (Ia) :

5



6. A process according to Claim 2, 3 or 4,
wherein R is of the formula (Ib) :

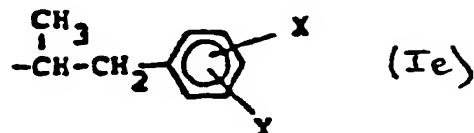
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7. A process according to Claim 2, 3 or 4,
wherein R is of the formula (Ic) :

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8. A process according to Claim 2, 3 or 4,
25 wherein R is of the formula (Id) :

30



35

9. A process according to Claim 2, 3 or 4,
wherein R is a cycloalkyl radical having from three to
eleven ring members, preferably from five to seven ring
members.

10. A process according to Claim 5, 6 or 7,

wherein X and Y are hydrogen.

11. A process according to Claim 10, wherein Q is 5'-deoxy- β -D-ribose and OR₂' and OR₃' are hydroxy or acetyl esters thereof.

5 12. A process according to Claim 11 when appendant to Claims 2 and 5, in which a compound having the following name is prepared :

5'-deoxy-N⁶-(2,2-diphenylethyl)adenosine.

10 13. A process according to Claim 11 when appendant to Claims 2 and 6, in which a compound having one of the following names is prepared :

5'-deoxy-N⁶-(1-indanyl)adenosine;

N⁶-1-tetralinyl-5'-deoxyadenosine; and

N⁶-1-tetralinyl-5'-deoxyadenosine-2',3'-di-O-acetyl.

15 14. A process according to Claim 11 when appendant to Claims 2 and 7, in which a compound having one of the following names is prepared :

(R)-5'-deoxy-N⁶-(1-methyl-2-phenylethyl)adenosine; and

(S)-5'-deoxy-N⁶-(1-methyl-2-phenylethyl)adenosine.

20 15. A process according to Claim 8 when appendant to Claim 2, in which a compound having one of the following names is prepared :

N⁶- α -naphthylmethyl-5'-deoxyadenosine; and

N⁶- α -naphthylmethyl-3'-deoxyadenosine-2',3'-di-O-

25 acetyl.

16. A process according to Claim 9 when appendant to Claim 2, wherein Q is 5'-deoxy- β -D-ribose and OR₂' and OR₃' are each hydroxy or acetyl esters thereof.

30 17. A process according to Claim 16, in which the following compound is prepared :

5'-deoxy-N⁶-(cyclopentyl)adenosine.

18. A process according to Claim 10, when appendant to Claim 3, wherein R₂' and R₃' are each independently hydrogen, acetyl, benzoyl or, when taken together, isopropylidene.

35 19. A process according to Claim 18, when

further appendant to Claim 5, in which the following compound is prepared :

5'-deoxy-5'-methylthio-N⁶-(2,2-diphenylethyl)adenosine.

20. A process according to Claim 18 when further appendant to Claim 6, in which the following compound is prepared :

5'-deoxy-5'-methylthio-N⁶-(1-indanyl)adenosine.

21. A process according to Claim 18 when further appendant to Claim 7, in which one of the following compounds is prepared :

(R)-5'-deoxy-5'-methylthio-N⁶-(1-methyl-2-phenylethyl)-adenosine; and

(S)-5'-deoxy-5'-methylthio-N⁶-(1-methyl-2-phenylethyl)adenosine;

22. A process according to Claim 9 when appendant to Claim 3, wherein R₂' and R₃' are each independently hydrogen, acetyl, benzoyl or, when taken together, isopropylidene.

23. A process according to Claim 22, wherein R₂' and R₃' are hydrogen.

24. A process according to Claim 23 in which a compound having the following formula is prepared :

5'-deoxy-5'-methylthio-N⁶-(cyclopentyl)adenosine.

25. A process according to Claim 10 when appendant to Claim 4, wherein R₂' and R₃' are each independently hydrogen, acetyl or benzoyl, or R₂' and R₃' when taken together are isopropylidene.

26. A process according to Claim 25 when further appendant to Claims 5, in which a compound having the following formula is prepared :

5'-deoxy-5'-chloro-N⁶-(2,2-diphenylethyl)adenosine.

27. A process according to Claim 25 when further appendant to Claim 6, in which one of the following compounds is prepared :

35 5'-deoxy-5'-chloro-N⁶-(1-indanyl)adenosine; and
(R)-N-6-(1-indanyl)-5'-deoxy-5'-chloro-adenosine.

28. A process according to Claim 25 when further appendant to Claim 7 in which one of the following compounds is prepared :

(R)-5'-deoxy-5'-chloro-N⁶-(1-methyl-2-phenylethyl)-adenosine; and

5 (S)-5'-deoxy-5'-chloro-N⁶-(1-methyl-2-phenylethyl)-adenosine

29. A process according to Claim 9 when appendant to Claim 4, wherein R₂' and R₃' are each independently hydrogen, acetyl, benzoyl or when taken together 10 an isopropylidene.

30. A process according to Claim 29, wherein R₂' and R₃' are each hydrogen.

31. A process according to Claim 30 in which the following compound is prepared :

15 5'-deoxy-5'-chloro-N⁶-(cyclopentyl)adenosine.

32. A process for preparing a pharmaceutical composition comprising combining a therapeutically effective amount of a compound prepared by a process as claimed in any preceding claim together with a pharmaceutically acceptable carrier or diluent.

20 33. For use in a method of treating psychoses in a mammal suffering therefrom, a compound prepared by a process as claimed in any one of Claims 1 to 31, preferably in unit dosage form.

25 34. For use in a method of treating hypertension in a mammal suffering therefrom, a compound prepared by a process as claimed in any one of Claims 1 to 31, preferably in unit dosage form.

30 35. For use in a method of treating pain in a mammal suffering therefrom, a compound prepared by a process as claimed in any one of Claims 1 to 31, preferably in unit dosage form.